

An Overview of Attention Deficit Hyperactivity Disorder



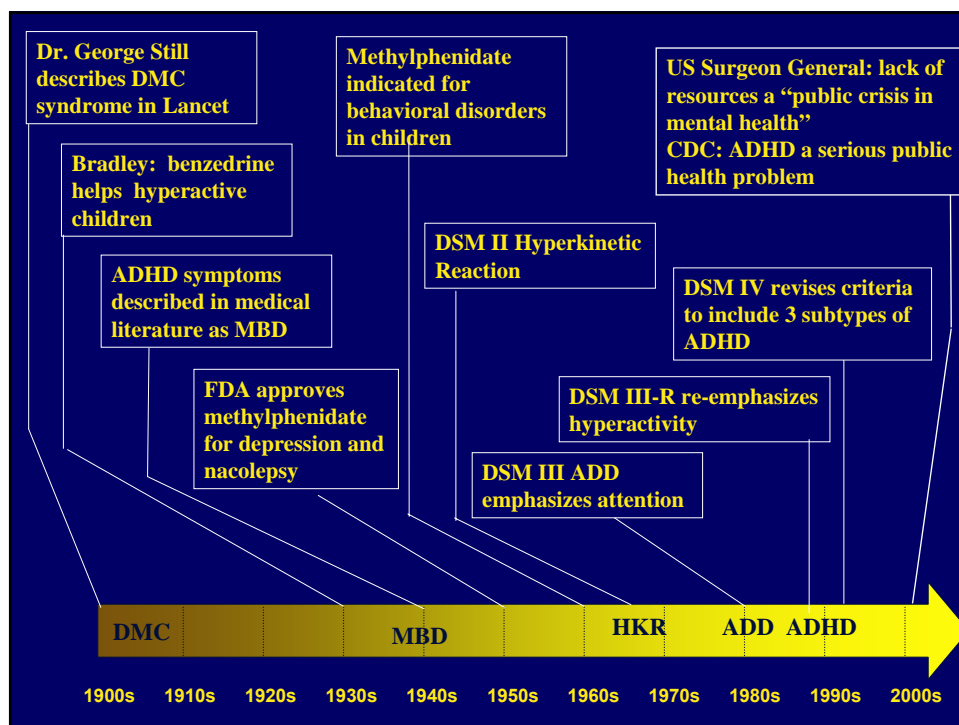
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Overview

- Clinical Features
- Impact
- Genes, Environment and ADHD

Clinical Features of ADHD



DSM-IV Criteria: Inattention

6 or more of the following—manifested *often*

- Inattention to details/ makes careless mistakes
- Difficulty sustaining attention
- Seems not to listen
- Fails to finish tasks
- Difficulty organizing
- Avoids tasks requiring sustained attention
- Loses things
- Easily distracted
- Forgetful

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Press; 1994.

DSM-IV Criteria: Impulsivity/Hyperactivity

6 or more of the following—manifested *often*

Impulsivity

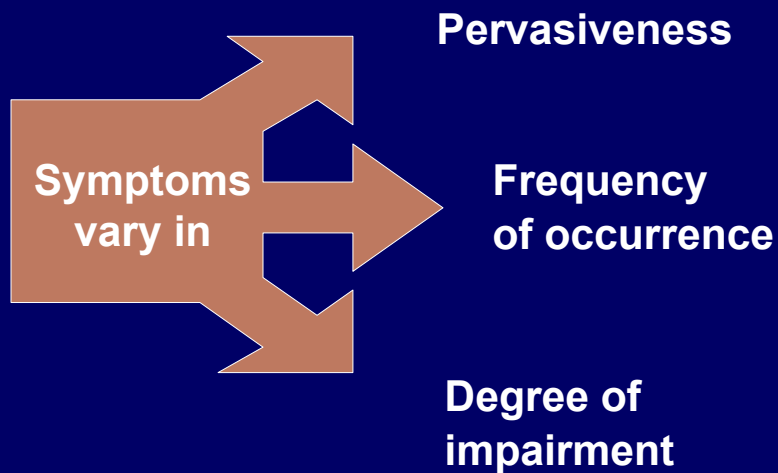
- Blurts out answer before question is finished
- Difficulty awaiting turn
- Interrupts or intrudes on others

Hyperactivity

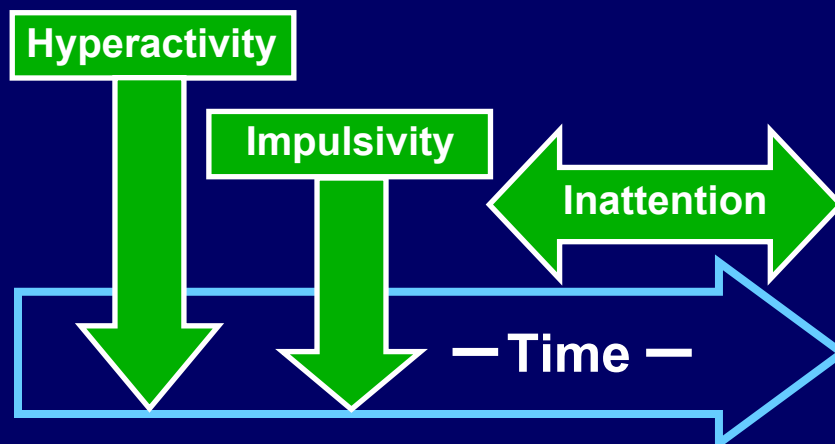
- Fidgets
- Unable to stay seated
- Inappropriate running/climbing (restlessness)
- Difficulty in engaging in leisure activities quietly
- “On the go”
- Talks excessively

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Press; 1994.

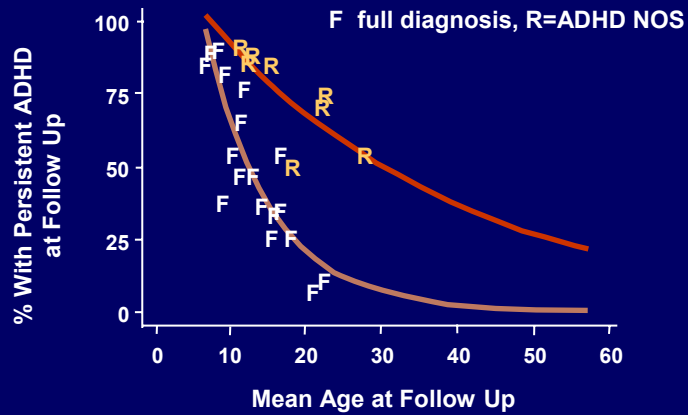
Variation in ADHD Symptoms



ADHD Symptoms Change in Adolescence and Adulthood

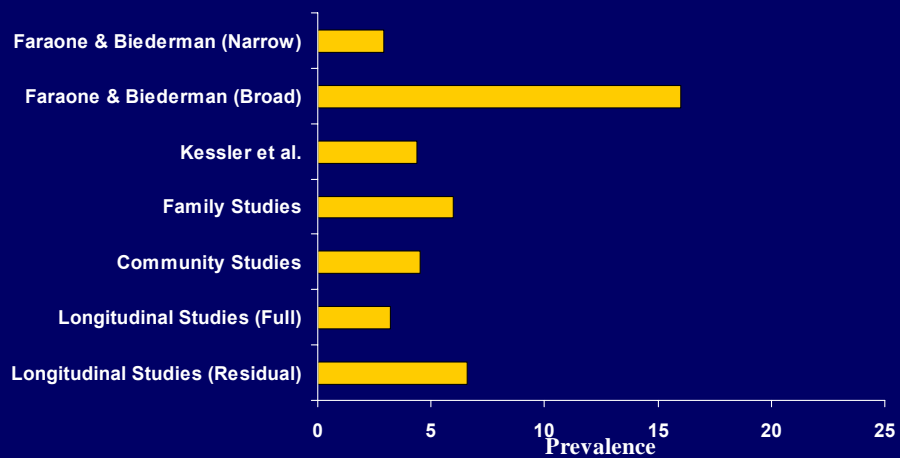


The Persistence of ADHD into Adulthood

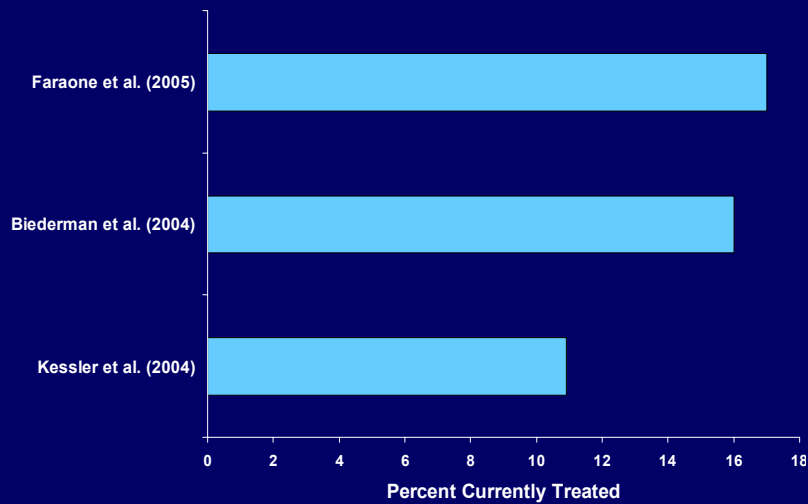


Faraone SV, et al. Psychological Medicine. In press.

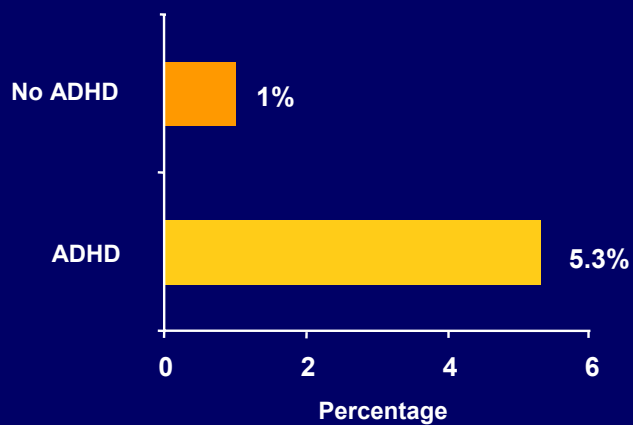
Summary: Prevalence of Adult ADHD



Adult ADHD: Common but Not Commonly Treated

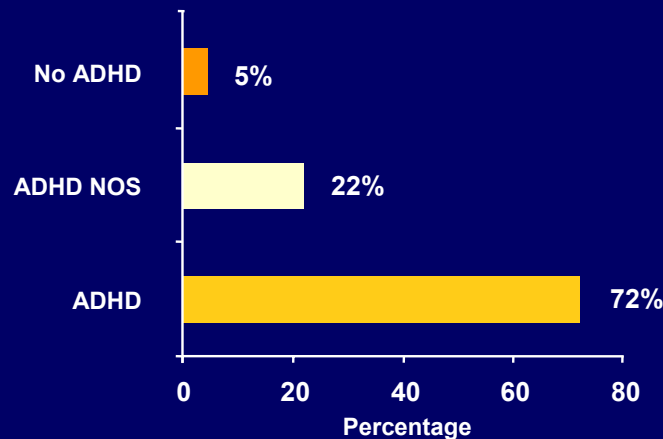


Treatment with Stimulants in the Community



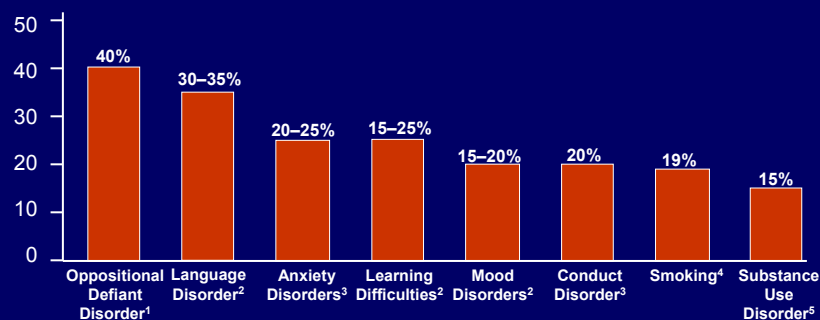
Szatmari, et al., *JAACAP*, 2000

Treatment with Stimulants: A Rural Community Study



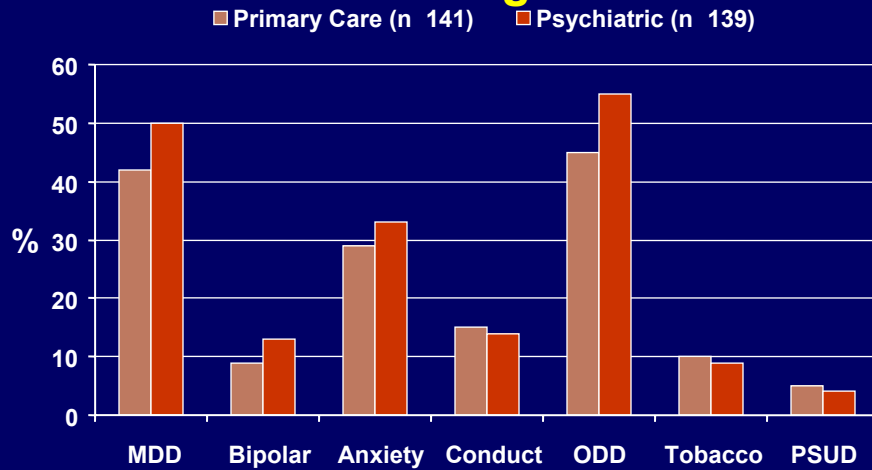
Angold, et al., *JAACAP*, 2000

ADHD: Pediatric Comorbid Conditions



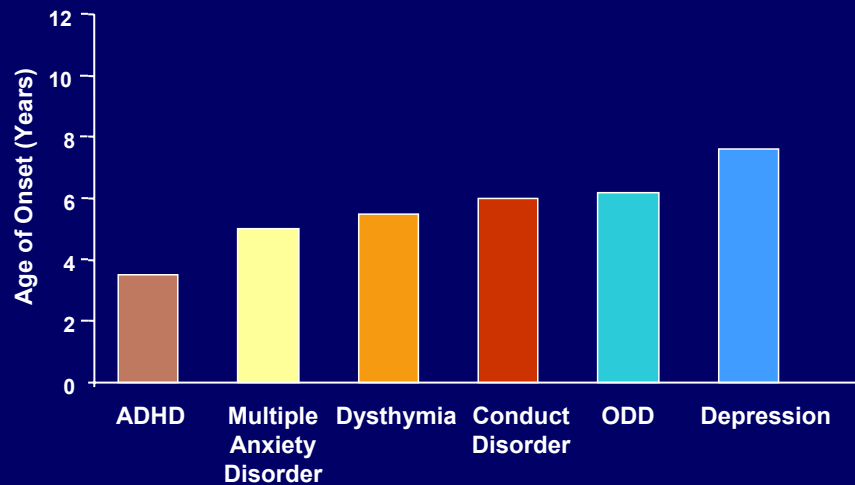
1. MTA Cooperative Group. *Arch Gen Psychiatry*. 1999 Dec;56(12):1073-86.
2. Barkley R. *Attention-deficit Hyperactivity Disorder. A Handbook for Diagnosis and Treatment*, 2nd ed. New York: Guilford Press; 1998.
3. Biederman J, et al. *Am J Psychiatry*. 1991 May;148(5):564-77.
4. Milberger S, et al. *J Am Acad Child Adolesc Psychiatry*. 1997 Jan;36(1):37-44.
5. Biederman J, et al. *J Am Acad Child Adolesc Psychiatry*. 1997 Jan;36(1):21-9.

Comorbidity in ADHD Youth from Primary Care and Psychiatric Settings



Busch B, et al. Psychiatr Serv. 2002 Sep;53(9):1103-11.

Developmental Progression of Comorbid Disorders



Biederman J, et al. Am J Psychiatry. 1993 Dec;150(12):1792-8.

Cognitive Comorbidity: Functions Impaired in ADHD

- Executive dysfunction
 - Filtering interfering stimuli
 - Maintaining focus and shifting attention when necessary
 - Sustaining attention
 - Inhibiting inappropriate responses
 - Organizing complex information

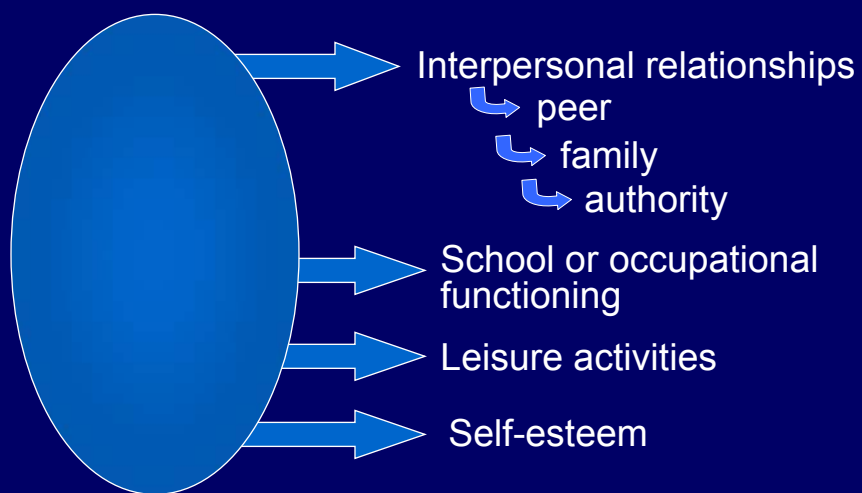
Cognitive Comorbidity: Functions Impaired in ADHD (cont'd)

- Executive dysfunction (cont'd)
 - Planning
 - Holding information in working memory
- Specific learning disorders
 - Reading, writing, math
 - Sequencing
 - Abstraction

Neuropsychological comorbidity is associated with learning disabilities, school failure, and poor socialization

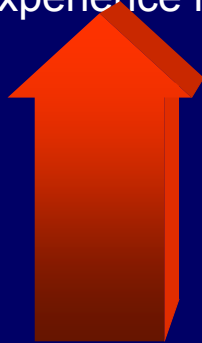
Impact of ADHD

Domains of Impairment



Impact on the Family

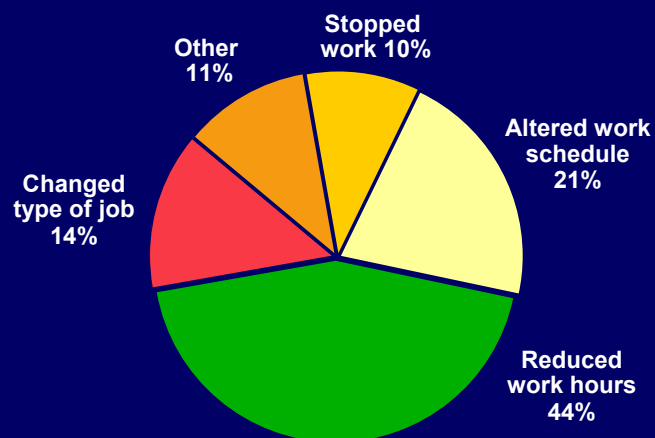
Parents of children with ADHD
experience higher:



- Stress
- Self-blame
- Social isolation
- Depression
- Marital discord

Mash & Johnston, *J Clin Child Psychol*, 1990;19:313.
Murphy & Barkley, *Am J Orthopsychiatry*, 1996;66:93.

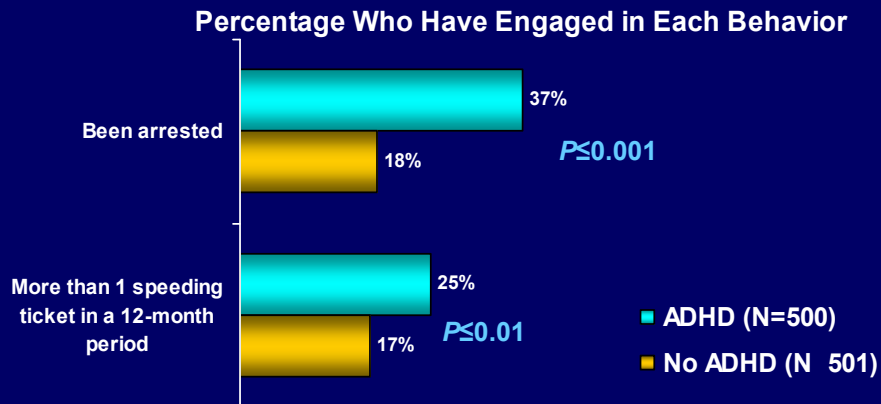
Types of Change in Work Due to Child's ADHD



Noe L. *J Managed Care Pharm.* 2001;7:133. Abstract.

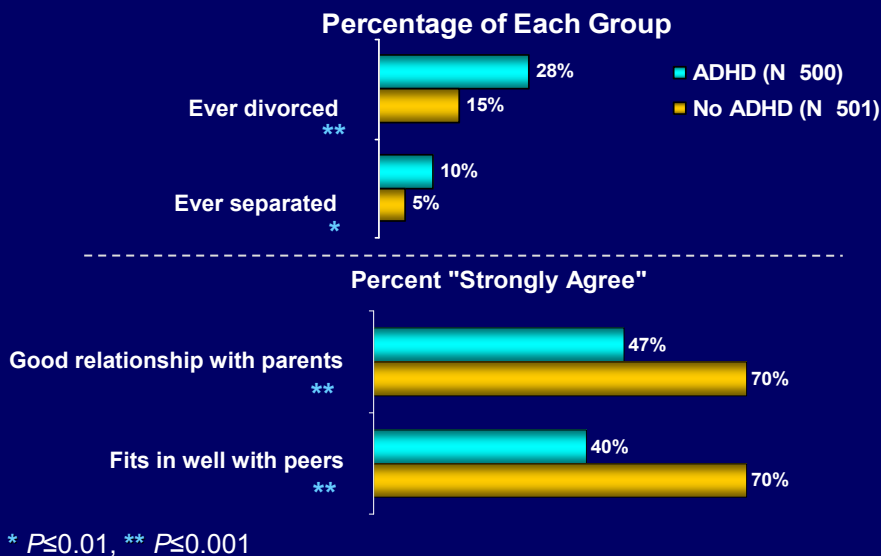
Arrests and Speeding Violations

(Biederman, Faraone et al., J Clin Psychiatry, 2006)



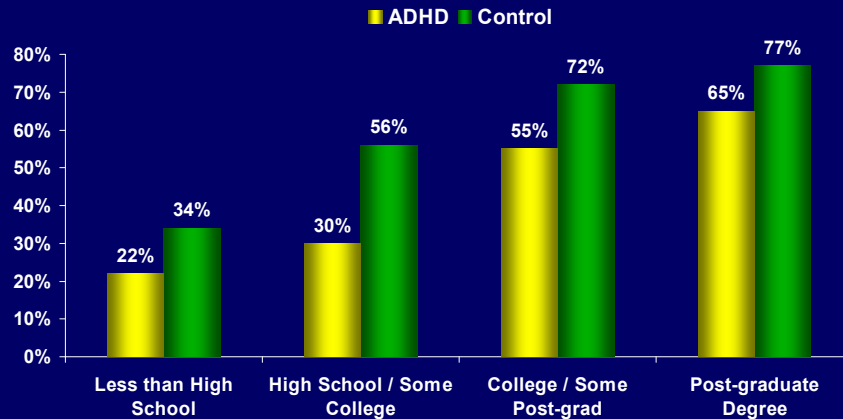
Relationship Problems as Adults

(Biederman, Faraone et al., J Clin Psychiatry, 2006)



Percent with Full-Time Employment by Academic Attainment

(Biederman, Faraone et al., J Clin Psychiatry, 2006)



Educational attainment is a factor in the difference in employment rates between those with ADHD and those without.

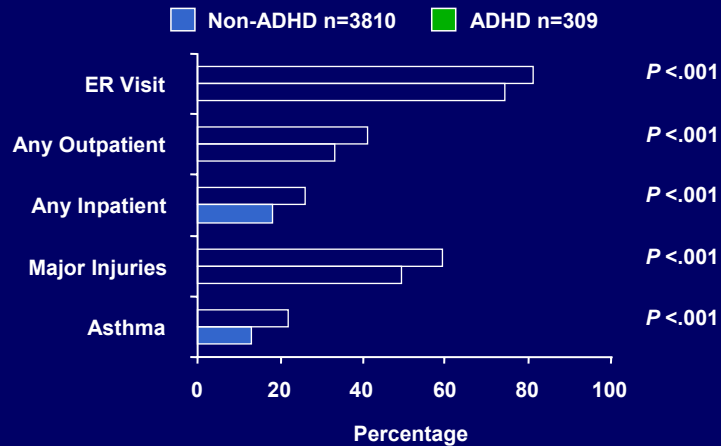
Statistically significant ($P < 0.001$) difference within educational categories.

Mean Yearly Household Income

(Biederman, Faraone et al., J Clin Psychiatry, 2006)

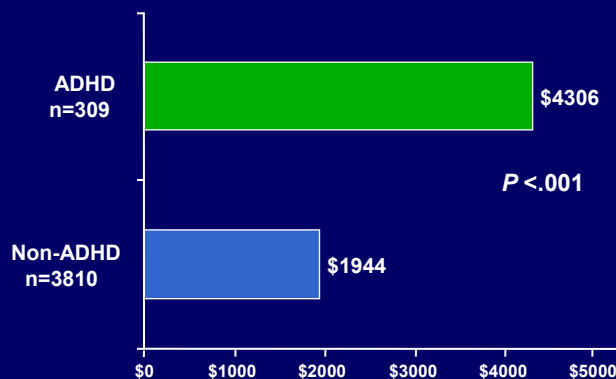
Parameter		ADHD (N=500)	Control (N=501)	P-value
Overall (\$)		41,511	52,053	<0.001
Sex (\$)	Male	45,645	54,399	<0.05
	Female	37,607	49,738	<0.001
Age (\$)	18-24	41,742	39,494	NS
	25-34	33,518	54,148	<0.001
	35-49	44,981	67,196	<0.001
	50-64	50,556	63,212	<0.05
Race (\$)	White / Caucasian	42,593	54,273	<0.001
	Non-White	32,750	46,030	<0.05
Marital Status (\$)	Married	50,806	64,928	<0.01
	Not Married	36,708	44,555	<0.05
Location (\$)	Urban	35,621	45,225	<0.05
	Rural	39,670	50,587	<0.05
	Suburban	51,501	61,427	<0.1

ADHD and Medical Care Use for Children and Adolescents in Minnesota, USA



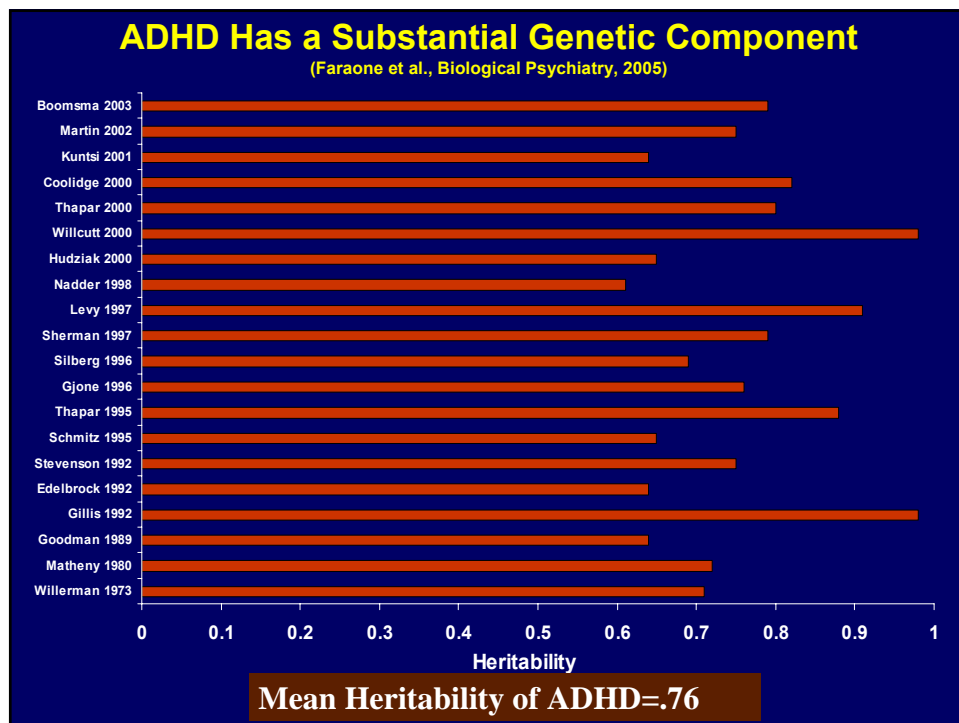
Leibson CL, et al. JAMA. 2001 Jan 3;285(1):60-6.

9-year Median Medical Costs for Children and Adolescents with and without ADHD



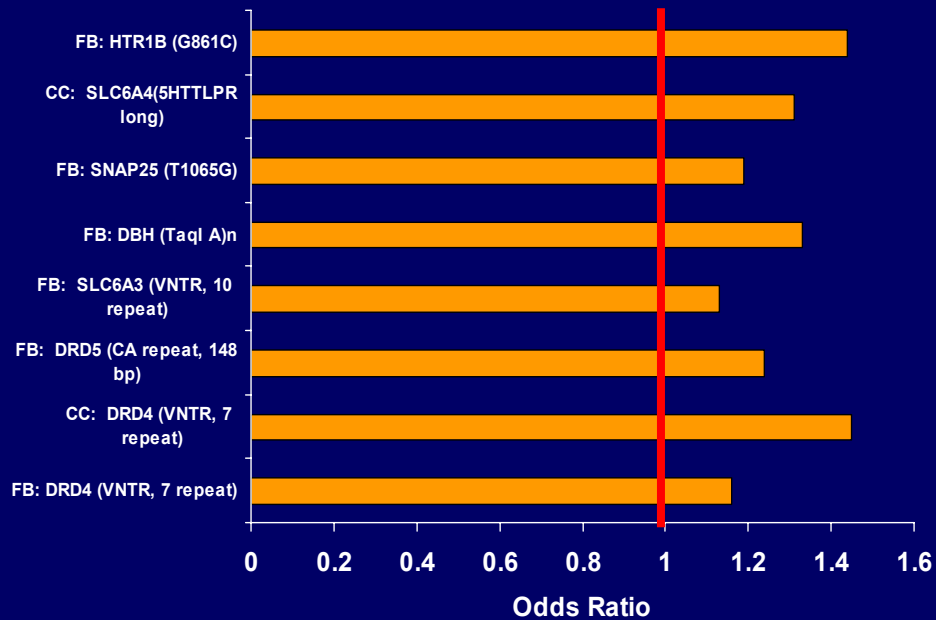
Leibson CL, et al. JAMA. 2001 Jan 3;285(1):60-6.

Genes, Environment and ADHD



ADHD is a Genetically Complex Disorder

(Faraone et al., Biological Psychiatry, 2005)



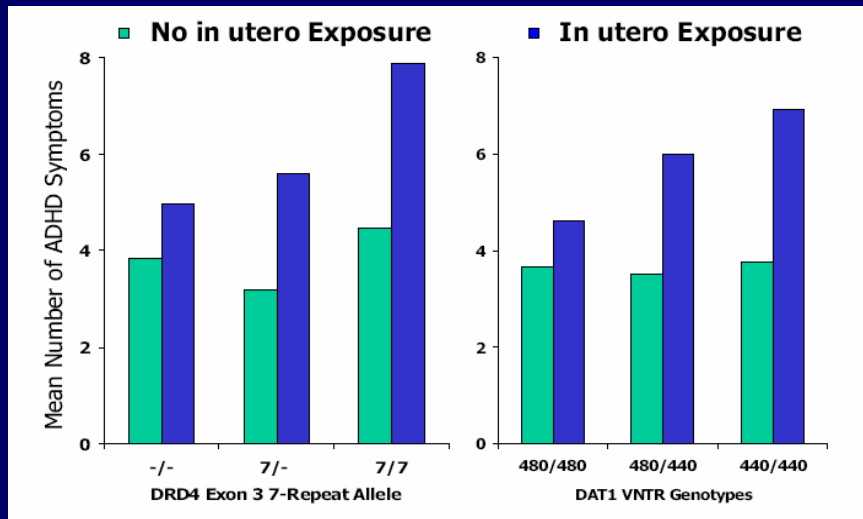
ADHD is an Environmentally Complex Disorder

(Banerjee, Middleton & Faraone, Acta Paediatrica, in press)

- Pregnancy and Delivery Complications
- Exposure to Toxins
 - ✓mercury, manganese, lead
 - ✓polychlorinated bi-phenyls
- Fetal exposure to alcohol
- Fetal exposure to maternal smoking
- Chaotic family environments
- Low social class

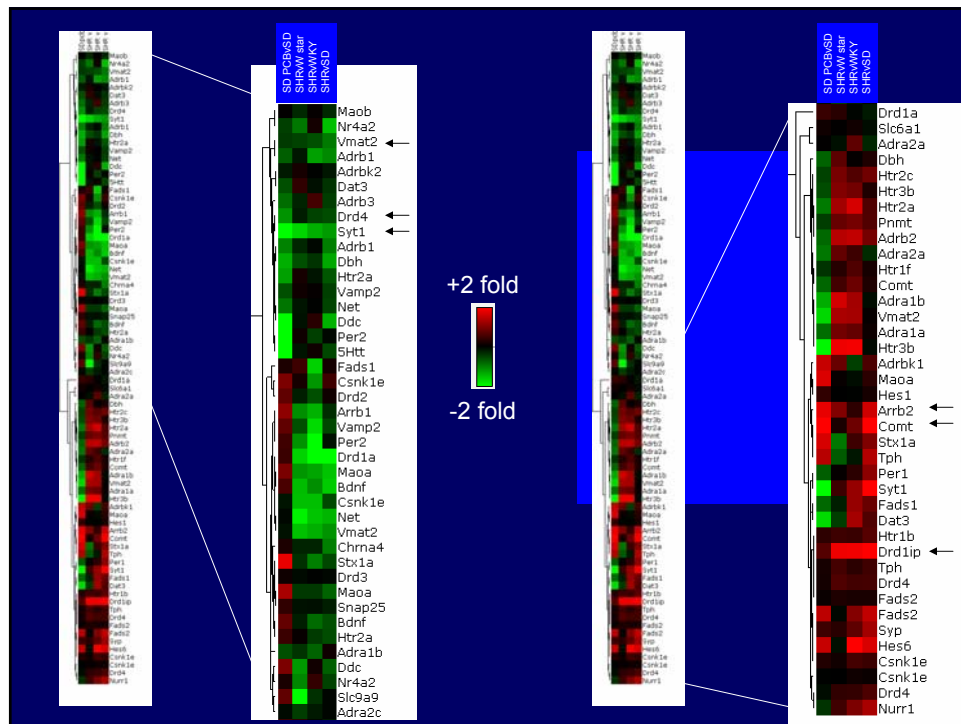
Maternal Smoking & ADHD Risk Genes

(Neuman et al., Biological Psychiatry, 2006)

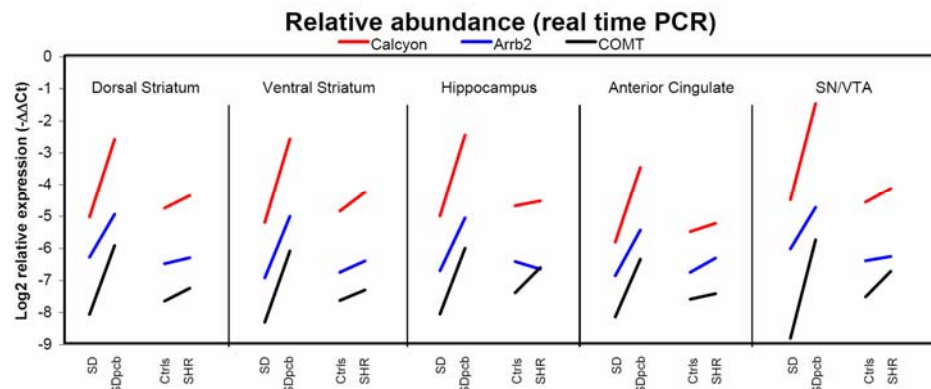


Animal Models of Genetic and Environmental Effects in ADHD

- Compare gene expression in 6 brain regions of rats
 - Genetic model of ADHD (SHR)
 - Environmental model of ADHD (*perinatal* PCB)
 - Q. Are the changes of ADHD candidate genes the same or different in the two models?
- Compare gene expression in brains of mice/rats in 2 experimental paradigms
 - *In utero* nicotine exposed (ongoing)
 - Developmental cigarette smoke exposed (with J. Zelikoff)
 - Q. Are the changes of ADHD candidate genes the same or different as those in rat models?



Validation of changes in expression using qRT-PCR on individual RNA samples for 3 increased genes



NB: Overall confirmation of 29/30 observations (should all have positive slope)
Also note that PCB effects confirmed as MORE robust than genetic model

Other genes validated: Synaptophysin, Period 2, Synaptotagmin

***in utero* cigarette exposure effects on IMAGE genes**

- Exposure to pregnant mouse dams equivalent to 1 pack/day, beginning at gestational day (GD) 4 thru GD 19
- No exposure after birth
- Examined IMAGE expression in 2 brain areas (SN-VTA, Vermis) in 8 young adult mice (4 male, 4 female)
- Focused on IMAGE genes with 2-fold changes

IMAGE gene probes with 2 fold changes

Probe Set ID	Gene Title	Symbol	Log2 Diff SN-VTA		Log2 Diff Vermis		Mean Diff
			Female	Male	Female	Male	
1423680_at	fatty acid desaturase 1	Fads1	1.53	5.26	4.26	2.34	3.35
1448280_at	synaptophysin	Syp	3.38	4.24	4.35	1.20	3.29
1452142_at	solute carrier family 6 (neurotransmitter transporter, GABA), member 1	Slc6a1	2.04	2.63	4.31	1.46	2.61
1436050_x_at	hairy and enhancer of split 6 (Drosophila)	Hes6	3.23	2.65	2.61	-0.48	2.01
1433884_at	synaptotagmin I	Syt1	2.11	2.93	2.46	0.48	1.99
1418701_at	catechol-O-methyltransferase	Comt	1.24	2.22	3.02	1.21	1.92
1420834_at	vesicle-associated membrane protein 2	Vamp2	3.11	2.94	1.30	0.27	1.91
1428813_a_at	dopamine receptor D1 interacting protein	Drd1p	3.14	3.65	0.45	-0.33	1.73
1417415_at	solute carrier family 6 (neurotransmitter transporter, dopamine), member 3	Slc6a3	3.16	4.38	-0.29	-0.59	1.66
1443838_x_at	fatty acid desaturase 2	Fads2	2.73	2.36	1.10	0.30	1.62
1419031_at	fatty acid desaturase 2	Fads2	2.54	2.18	1.25	-0.47	1.37
1426215_at	dopa decarboxylase	Ddc	2.19	2.90	0.20	0.03	1.33
1420833_at	vesicle-associated membrane protein 2	Vamp2	1.72	1.88	0.55	0.29	1.11
1428667_at	monoamine oxidase A	Maoa	1.19	1.30	1.05	0.50	1.01
1434450_s_at	adrenergic receptor kinase, beta 2	Adrbk2	0.68	1.42	1.04	0.79	0.98
1437079_at	solute carrier family 18 (vesicular monoamine), member 2	Slc18a2	2.41	2.03	-0.87	-0.14	0.86
1449183_at	catechol-O-methyltransferase	Comt	1.84	0.95	0.50	-0.21	0.77
1434354_at	monoamine oxidase B	Maob	0.02	2.34	-0.04	0.66	0.75
1433719_at	solute carrier family 9 (sodium/hydrogen exchanger), isoform 9	Slc9a9	1.17	1.09	0.35	0.31	0.73
1417602_at	period homolog 2 (Drosophila)	Per2	0.75	1.40	0.72	0.04	0.73
1418932_at	nuclear factor, interleukin 3, regulated	Nfil3	1.35	1.12	0.45	-0.30	0.66
1440801_s_at	adrenergic receptor kinase, beta 2	Adrbk2	1.19	0.91	0.05	0.15	0.57
1426239_s_at	arrestin, beta 2	Arnb2	0.62	1.74	0.19	-0.30	0.56
1418950_at	dopamine receptor 2	Drd2	1.35	0.94	-1.08	-0.18	0.26
1435513_at	5-hydroxytryptamine (serotonin) receptor 2C	Htr2c	-0.01	0.54	-1.08	0.80	0.01
1433600_at	adrenergic receptor, alpha 2a	Adra2a	-0.75	0.49	-1.14	0.29	-0.28
1422830_s_at	dopamine receptor 4	Drd4	-0.19	-1.23	0.10	-0.11	-0.36
1450477_at	5-hydroxytryptamine (serotonin) receptor 2C	Htr2c	-0.39	-0.41	-1.07	-0.21	-0.52
1438282_at	synaptotagmin I	Syt1	-0.75	-1.10	-0.65	-0.04	-0.63
1437302_at	adrenergic receptor, beta 2	Adrb2	-1.11	-0.92	-0.98	0.22	-0.70
1422169_a_at	brain derived neurotrophic factor	Bdnf	-1.19	-1.11	-0.51	-0.82	-0.91
1442557_at	synaptotagmin I	Syt1	-0.75	-1.32	-0.58	-1.18	-0.96
1449804_at	phenylethanolamine-N-methyltransferase	Pnmt	-0.88	-1.50	-0.91	-0.71	-1.00

Note: MANY IMAGE genes are affected

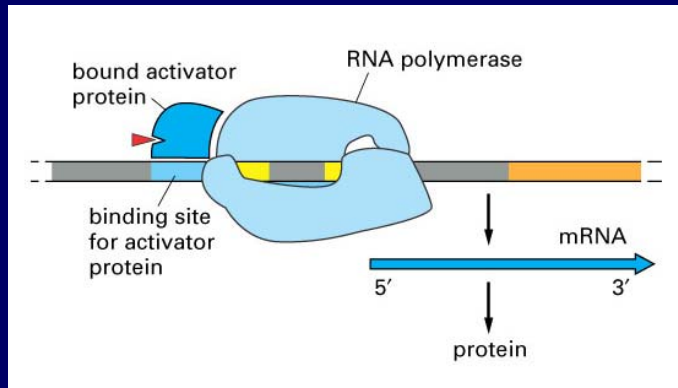
Environmental Regulation of Gene Expression

Gene expression depends on:

can RNA polymerase II access the promoter?

is the DNA bound to histone proteins acetylated or de-acetylated?

are the CpG islands near the gene methylated or unmethylated?



From Essential Cell Biology, 2nd Ed, Garland Press, 2004

Epigenetic gene probes with 2 fold changes

Gene Title	Symbol	Log2 Diff SN-VTA Female	Log2 Diff SN-VTA Male	Log2 Diff Vernis Female	Log2 Diff Vernis Male	Mean Diff
Sin3-associated polypeptide 18	Sap18	2.20	3.12	2.79	1.32	2.36
histone deacetylase 11	Hdac11	2.34	4.28	2.20	0.36	2.29
Sin3-associated polypeptide 18	Sap18	1.51	2.17	2.37	1.53	1.90
CREB binding protein	Crebbp	2.34	1.77	2.92	0.42	1.86
p300/CBP-associated factor	Pcaf	0.87	1.76	3.46	1.35	1.86
MYST histone acetyltransferase 2	Myst2	2.55	3.10	1.05	0.04	1.69
Sin3-associated polypeptide 18	Sap18	1.51	2.03	1.71	0.55	1.45
methyl-CpG binding domain protein 2	Mbd2	0.83	1.34	1.43	1.62	1.31
Sin3-associated polypeptide 18	Sap18	1.73	1.40	1.57	-0.18	1.13
histone deacetylase 11	Hdac11	0.77	1.37	0.82	0.71	0.92
histone deacetylase 6	Hdac6	1.24	1.60	0.38	0.28	0.88
methyl-CpG binding domain protein 1	Mbd1	1.59	0.78	0.57	0.18	0.78
histone deacetylase 5	Hdac5	1.66	1.09	0.54	-0.30	0.72
DNA methyltransferase (cytosine-5) 1	Dnmt1	-0.44	-0.30	1.36	2.28	0.72
DNA methyltransferase 1-associated protein 1	Dmap1	1.14	1.23	0.23	0.00	0.65
methyl CpG binding protein 2	Mecp2	-0.09	0.38	0.70	1.51	0.62
GCN5 general control of amino acid synthesis-like 2 (yeast)	Gcn5l2	1.70	0.68	0.13	-0.09	0.61
methyl-CpG binding domain protein 3	Mbd3	1.39	0.53	0.43	-0.19	0.54
MYST histone acetyltransferase (monocytic leukemia) 3	Myst3	-0.14	1.00	-0.02	1.15	0.49
Sin3-associated polypeptide 18	Sap18	1.36	-0.11	0.48	-0.09	0.41
histone deacetylase 3	Hdac3	1.18	0.40	0.09	-0.24	0.36
DNA methyltransferase 3A	Dnmt3a	1.22	-0.21	-0.25	-0.13	0.16
methyl CpG binding protein 2	Mecp2	-0.71	-1.49	0.09	0.39	-0.43
p300/CBP-associated factor	Pcaf	-0.77	0.01	-1.17	-0.28	-0.55
DNA methyltransferase 3B	Dnmt3b	-1.65	-0.55	-0.69	0.46	-0.61
MYST histone acetyltransferase (monocytic leukemia) 3	Myst3	-1.19	-0.34	-1.02	-0.15	-0.67
histone deacetylase 10	Hdac10	-1.98	0.22	-1.98	0.65	-0.77
MYST histone acetyltransferase 2	Myst2	-0.43	-1.78	0.00	-1.07	-0.82
histone deacetylase 2	Hdac2	-1.13	-1.52	-0.53	-0.99	-1.04
histone deacetylase 2	Hdac2	-3.04	-2.28	-1.30	1.28	-1.34

Summary

- Clinical Features
 - Hyperactivity, Impulsivity Intention
 - Psychiatric Comorbidity
 - Neuropsychological Dysfunction
 - Course into Adulthood
- Adverse impacts of ADHD seen in
 - School
 - Socialization
 - Driving
 - The workplace

Developmental Progression of ADHD

